Costa J, Espirito-Santo CC, et al. Botulinum toxin type A therapy for cervical dystonia (Review). Cochrane Database of Systematic Reviews 2005, Issue 1, Art. No. CD003633.

Design: Meta-analysis of randomized clinical trials

PICOS:

- **Patients**: any patients with clinical diagnosis of cervical dystonia
- **Intervention**: Intramuscular injection with botulinum toxin A (BtA)
- **Comparison**: Placebo injection
- **Outcomes**: Improvement in symptomatic rating scales (primary outcome); secondary outcomes include changes in subjective evaluation of clinical status by patient or clinician; changes in pain scores, changes in quality of life assessments; adverse reactions to injection
- **Study designs**: Randomized, controlled, blinded trials with adequate concealment of allocation

Study search and selection:

- Databases for search were Cochrane Movement Disorders register, Cochrane Controlled Trials register, MEDLINE and EMBASE (1977 to June 2003), abstracts of international congresses of movement disorders, personal communication with authors, other researchers, and drug manufacturers
- Three reviewers assessed studies for sources of bias (selection, performance, attrition, detection, selective reporting of results), with disagreements resolved by discussion
- 13 studies were selected for inclusion into the review; 8 studies were excluded

Results:

- Of the 13 studies included for meta-analysis, 5 had a parallel group design and 8 had crossover design; for crossover studies, only data from the first period were used for efficacy assessments
- Trials used different commercial preparations and injection techniques; 8 used Botox and 5 used Dysport; 7 studies used free hand injection and 6 used EMG guidance
- The mean Botox dose was 188U; the mean Dysport dose was 577U
- Risk of bias in the included studies was considered low on factors like selection bias, blinding, performance bias, and attrition bias
- The commonest outcome scale was the Tsui scale, which combines scores for tilt, rotation, shoulder elevation, and head tremor into a single number from 0 to 25 (most severe)
- Many analyses were done using different outcome definitions; BtA was more effective than placebo on most outcomes
- For example, using the outcome of a 3 point improvement in the Tsui scale, the relative benefit of BtA over placebo was 4.25 (95% confidence interval 2.0 to 9.1)

- For the patient's subjective report of improvement, the relative benefit of BtA was 6.58 (95% confidence interval 4.55 to 9.54)
- Both therapeutic and adverse effects were dose-related
- Adverse effects significantly associated with BtA were neck weakness (relative risk 4.9), dysphagia (RR 3.9), dry mouth/sore throat (RR 2.5); the RR for voice changes/hoarseness was 2.6 but the 95% confidence interval was from 0.98 to 7.0 and did not reach conventional statistical significance; these adverse effects were transient and mild to moderate in severity
- For other adverse events (drowsiness, vertigo, dizziness, diffuse weakness, tiredness, malaise) there were not significant differences between BtA and placebo
- Indirect comparisons between Botox and Dysport preparations showed no significant differences in efficacy and safety
- Only 3 studies looked for neutralizing antibodies in patients previously treated with BtA; about 15% of these patients had neutralizing antibodies to BtA

Authors' conclusions:

- BtA produced clinically and statistically significant improvements in pain and disability
- Two large trials enrolled patients already known to respond to BtA; this is likely to improve the chances of a positive trial
- Subjective outcome measures were generally greater than outcomes based on objective scales; this may be more important to patients than objective benefits
- There is a clear dose-response relationship for beneficial and adverse effects
- The duration of effect of BtA and its immunogenicity were not established
- No differences were established between Botox and Dysport
- BtA injections are well tolerated and rarely severe

Comments:

- Combining parallel group and crossover trials is acceptable when the first period data of the crossover trial are used; this may weaken the power of the analysis but is not expected to bias the answer, and the authors appear to have used the data correctly
- Some of the analyses (e.g., "any subjective improvement") allow a larger number of trials to be combined, but the precision of the relative benefit must be interpreted cautiously
- The forest plot of the same analysis of :subjective improvement" (Analysis 2.1, Comparison 2) shows all 11 effects favoring BtA, 9 of them statistically significant
- The forest plot of the adverse effects of dysphagia and neck weakness (Analysis 5.2, Comparison 3) also show all effects favoring placebo, but only one or two are statistically significant

Assessment: For objective and symptomatic benefits of BtA over placebo: strong evidence For transient dysphagia and neck weakness: good evidence. Overall adequate – high-quality.